Differential Expression of Lymphocyte Function-Associated Antigen 1 (LFA-1) on Epidermotropic and Non-Epidermotropic T-Cell Clones

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Various T-cell surface molecules are involved in T-cell adhesion, which is an essential requirement for epidermotropic migration of T cells. Our previous studies demonstrated that certain T-cell clones can migrate into the epidermis upon their intradermal inoculation into the footpads of recipient mice with relevant antigens, while other T-cell clones, despite their identical antigen specificities and functions, are non-epidermotropic. We therefore tested whether the differences in epidermotropism of these T cells could reside in the different levels of expression of T-cell surface molecules such as CD3, CD4, CD2, and lymphocyte function associated antigen 1 (LFA 1). The results of flow cytometric analysis showed that LFA-1 was preferentially expressed on the surface of epidermotropic T-cell clones, while non-epidermotropic T-cell clones were negative or very weakly positive for LFA-1 with one exception. After exposure to phorbol ester, epidermotropic clones with high levels of LFA-1 did not show any further up-regulation of LFA-1. In contrast, under identical conditions, significant up-regulation of LFA-1 was observed on non-epidermotropic T cells with low levels of LFA-1. However, even after exposure to phorbol ester, these T cells remained non-epidermotropic. These results suggest that the presence of high levels of LFA-1 on T cells is absolutely necessary for their epidermotropic migration, but its up-regulation is neither necessary nor sufficient to trigger the epidermotropic migration. High levels of LFA-1, regardless of cell activation, may be required to mediate stable cell adhesions leading to epidermotropic migration.
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In various skin diseases where T-cell-mediated mechanisms are thought to be involved, T cells show a specific affinity for the epidermis, known as epidermotropism [1]. Although lymphocyte migration into lymphoid tissue has been extensively studied and the receptor-ligand type of interaction between lymphocytes and postcapillary high endothelial venules (HEV) has been proved to be essential for the ability to migrate into lymphatic tissue [2], much less is known about the factors that govern T-cell trafficking in the skin. Most of the recent studies have suggested that migration of lymphocytes into the epidermis may require specific binding of the lymphocytes to the epidermal keratinocytes, the recognition of which is that the receptor-mediated interaction is different from lymphocyte-HEV recognition systems. The adherence between lymphocytes and interferon γ (IFN-γ)-treated keratinocytes involves lymphocyte function-associated antigen 1 (LFA-1) on the lymphocytes and intercellular adhesion molecule 1 (ICAM-1) on the keratinocytes, a ligand for LFA-1 [3-5].

We previously demonstrated that $CD4^+$ cloned T cells specific for self- or allo-I-A can migrate into the epidermis following their intradermal inoculation into the footpads of syngeneic or allogeneic mice with the relevant I-A antigens, and cause the destruction of the epidermis, the histology of which closely resembles cutaneous graft-versus-host disease (GVHD) [6,7]. In contrast, other $CD4^+$ cloned T cells, despite their identical antigen specificities and functions, are completely unable to migrate into the epidermis under identical conditions [6,7]. Thus, the demonstrated migration differences among these T cells cannot be explained on the basis of the antigen specificities and functions. Interestingly, in vivo administration of monoclonal antibodies (MoAb) directed against LFA-1 and CD4 blocked the epidermotropic migration and the subsequent destruction of the epidermis [8]. These results prompted us to test whether the differences in epidermotropism of these T cells could reside in the different levels of expression of cell surface molecules that are involved in T-cell adhesion. We present evidence here that the presence of LFA-1 on T cells is necessary but not sufficient to render the T cells capable of migrating into the epidermis, but that up-regulation of the LFA-1 is neither necessary nor sufficient to induce epidermotropism of stimulated lymphocytes.

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Abbreviations:
B6: C57BL/6
GVHD: graft-versus-host disease
ICAM-1: intercellular adhesion molecule 1
IFN-γ: interferon γ
MoAb: monoclonal antibody
PKC: protein kinase C
PMA: phorbol 12-myristate 13-acetate
TCR: T cell receptor

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MATERIALS AND METHODS

Mice Female C57BL/6 (B6), C57BL/10 (B10), and Balb/c mice were obtained from Charles River Japan, Inc. and maintained in our animal facility. They were used predominantly at 8–12 weeks of age.

Cloned T Cells The general characteristics of the cloned T cells used are shown in Table I. The derivation of these cloned T cells has been previously described in detail [6,9,10]. BB5, SK1, and J403 cells are capable of migrating into the epidermis upon their intradermal inoculation into the footpads of the syngeneic (in case of BB5) or appropriate allogeneic recipients with I-$A^{k,b,f,r}$ molecules (in case of SK1) or with H-$2K^b$ (in case of J403) and cause the destruction of the epidermis [6,7]. In contrast, other cloned T cells are totally non-epidermotropic [6,7]. These T cells were maintained by weekly feedings with mitomycin C-treated syngeneic (BB5, C10) or appropriate allogeneic (SK1, SK2.16, SK2.18 and J403) spleen cells and rat interleukin 2 (IL-2). Clone 82F12 was maintained in the same manner but with 250 μg/ml chicken γ-globulin (CGG).

MoAb Our panel of MoAb used in this study is described in Table II. MoAb 145-2C11 [11], GK1.5 [12], and M17/4.2 [13] were kind gifts of Dr. C. Janeway Jr. (Yale University, CT). 53-6.7 [14] and M1/70 [15] were purchased from Becton Dickinson (Mountain View, CA) and Hybritech Inc. (San Diego, CA), respectively. Anti-murine CD2 was raised at the Department of Immunology, Juntendo University (Tokyo, Japan), and the detailed characterization will be reported elsewhere [16].

Flow Cytometric Analysis Saturating concentration of all MoAb used in this analysis was predetermined on appropriate antigen-bearing cells. Cloned T cells (2×10^6) were incubated with 0.1 ml of the appropriately diluted primary MoAb for 45 min at 4°C. After two washes with PBS containing 5% heat-inactivated fetal bovine serum (FBS) and 0.02% sodium azide, the cells were reincubated at 4°C for 45 min with fluorescein isothyocyanate (FITC)-conjugated goat $F(ab')_2$ anti-mouse, rat, or hamster IgG antibody (Tago, Burlingame, CA) diluted 1:20 in PBS. After two additional washes, the cells were resuspended in 0.2 ml of PBS containing 0.02% sodium azide and analyzed by an Epics C flow cytometer (Coulter Electronics, Hialeah, FL). As a control, the cells were stained with nonrelevant MoAb of identical isotypes, followed by second antibody. The fluorescence intensity of the positive cells was expressed as the arbitrary unit plotted on a logarithmic scale.

Treatment with Phorbol Ester Phorbol 12-myristate 13-acetate (PMA) was purchased from Sigma (St. Louis, MO). Stock solutions were prepared in DMSO and stored at −70°C. Prior to addition to cell culture, PMA was diluted in medium to an appropriate concentration. In all experiments with PMA, the final concentration of DMSO in cell culture was less than 0.1%v/v.

Evaluation of the Migration of T Cells into the Epidermis The T cells treated with or without PMA were harvested at 48 h. Before the T cells were used in experiments, dead cells in the preparation were removed on a lymphocyte separation media (Sigma Chemical Co., St. Louis, MO) density gradient, and the remaining cells were washed three times with Hanks' balanced salt solution (HBSS). Then the T cells (2×10^6) with a viability of more than 97% were injected intradermally, in a volume of 25 μl, into hind footpads of naive syngeneic or allogeneic mice, as previously described [6–8]. Footpad skin specimens were taken from mice at 96 h after they received the T cells, and formalin-fixed, hematoxylin-eosin stained sections were prepared to evaluate the migration of the T cells into the epidermis. The semi-quantitative evaluation of the migration was performed by counting lymphoid cells within the epidermis, as previously described [8]. In parallel, the severity of the epidermal cell damage was scored according to the grading system described by Lerner et al [8] for cutaneous GVHD. At least 30 serial sections were examined for each individual footpad. Of these, six sections in which the epidermis was regarded to be most heavily infiltrated with lymphoid cells were evaluated in a blind fashion by two investigators who were uninformed of the treatment.

Table II. Panel of Monoclonal Antibodies Used in this Study

Designation	Isotype	Specificity
145-2C11	Hamster IgG	CD3
RM2-1	Rat IgG	CD2
GK1.5	Rat IgG 2b	CD4 (L3T4)
53-6.7	Rat IgG 2a	CD8 (Lyt-2)
M17/4.2	Rat IgG 2a	LFA-1α
M1/70	Rat IgG 2b	Mac-1

RESULTS

Expression of LFA-1 on Epidermotropic or Non-Epidermotropic T-Cell Clones in the Resting State In addition to antigen-specific binding mediated by the T-cell receptor (TCR)-CD3 complex, a number of other molecules expressed on the T-cell surface are involved in the regulation of T-cell adhesion [17]. Recent studies have led to the suggestion that the inability of non-epidermotropic T cells to migrate into the epidermis is due in part to the lack of or decrease in expression of lymphocyte surface molecules necessary for cell-cell or cell-matrix interactions. To test this possibility, various cloned T cells, including epidermotropic (BB5, SK1 and J403) and non-epidermotropic (C10, 82F12, SK2.16 and SK2.18) T cells, were analyzed for their expression of various lymphocyte surface molecules.

Flow cytometric analysis was performed with resting T-cell clones harvested 3–5 d after their last exposure to specific antigens and IL-2. Figure 1 shows the results of representative flow cytometric analysis of seven T-cell clones stained with MoAb directed against CD3, CD4, CD8, CD2, and LFA-1. All clones were positive for CD3, and all class II-restricted T cells were strongly positive for CD4 expression, while class I-restricted T cells were CD8 positive. There was little difference in the fluorescence profiles of CD3 and CD4 among cloned T cells tested, regardless of their epidermotropic capacity. In contrast, they exhibited various levels of LFA-1 expression, which correlated with the epidermotropic nature of the

Table I. Description of T-Cell Clones Used in this Study

Clone designation	Source	Strain of origin	Antigen specificity	Function	Epidermotropism
BB5	LN*	B6	I-A^b (self)	Cytotoxic/Helper	+++
C10	Spleen	B6	I-A^b (self)	Cytotoxic/Helper	−
82F12	LN*	B6	CGG + I-A^b	Helper	−
SK1	Spleen	A.TH	I-$A^{k,b,f,r}$	Cytotoxic/Helper	++
SK2.16	Spleen	A.TH	I-$A^{k,s}$	Helper	−
SK2.18	Spleen	A.TH	I-A^k, I-E^k	Cytotoxic/Helper	−
J403†	Spleen	B10.BR	H-$2K^b$	Cytotoxic	+ ~ ++

* Lymph node.
† Uncloned T-cell line.

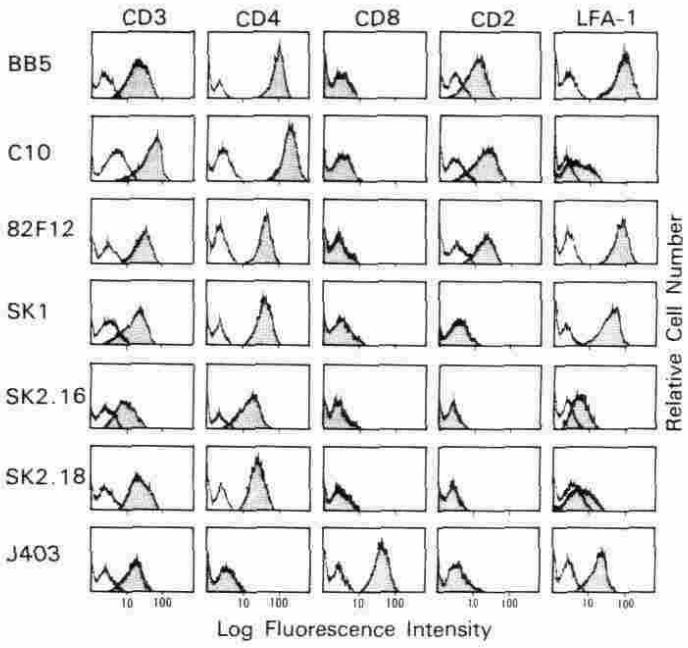

Figure 1. Flow cytometric analysis of surface expression of CD3, CD4, CD8, CD2, and LFA-1 by resting T-cell clones. The cells were stained for the indicated MoAb by the indirect fluorescence method and analyzed on the flow cytometer. Each histogram shows the analysis of 5,000 cells. *Thin lines* represent control staining with nonrelevant primary MoAb, followed by FITC-conjugated second Ab.

clones with an exception of 82F12. All epidermotropic T cells, BB5, SK1 and J403, showed intense reactivity with anti-LFA-1, while non-epidermotropic T cells, C10, SK2.16, and SK2.18, were negative or very weakly positive for LFA-1 expression. One non-epidermotropic clone, 82F12, however, expressed high levels of LFA-1 comparable to those of BB5 and SK 1. Although the level of CD2 expression varied from clone to clone, it appeared that there was no apparent correlation between CD2 expression and the epidermotropic capacity of these clones: C10 and BB5 showed equivalent surface expression of CD2, and SK1 was negative for CD2, but nevertheless retained significant migratory activity. No cells showed specific staining with anti-Mac-1 MoAb (data not shown).

Alterations in LFA-1 Expression of the T-cell Clones Upon Activation Our previous studies indicate that upon activation the epidermotropic T-cell clones become motile and acquire the ability to migrate into the epidermis [6,7,18]. Because the expression of various lymphocyte membrane molecules has been shown to modulate after cell activation [19,20], it was possible that the expression of these surface molecules observed with these T cells in the resting state may not necessarily reflect the possible modulation of these molecules that may occur in vivo as a result of cell activation. We therefore asked whether LFA-1 expression during cell activation could correlate with the ability of the T cells to migrate into the epidermis. It has been shown that increases in T-cell adhesions are induced by phorbol esters, perhaps by bypassing specific activation mechanism through direct stimulation of protein kinase C (PKC) [21] and that the increases are sometimes, but not always, accompanied by increases in LFA-1 density [22,23]. BB5, C10, and 82F12 cells were therefore activated by exposure to various concentrations of PMA. After the time period indicated the cells were harvested and dead cells were removed on a lymphocyte separation media, as previously described [7,8]. Then the remaining cells were stained for flow cytometric analysis. As shown in Fig 2, exposure of C10 cells to PMA at 50 ng/ml resulted in a significant up-regulation of surface LFA-1, as judged by the degree of the increase in mean fluorescence intensity: a fivefold increase at 48 h. The PMA-induced up-regulation of LFA-1 on C10 cells appeared to be a dose-dependent phenomenon, because 20–50 ng/ml of PMA induced the most consistent up-regulation of the LFA-1, while no significant changes were observed at <1 ng/ml. The LFA-1 expression on C10 cells after a 48-h exposure to PMA was almost equivalent to that on J403 cells at either the resting or activating state. In general, T cells expressing low levels of LFA-1 in their resting state, such as SK2.16 and SK2.18 cells, exhibited similar up-regulation of LFA-1 48 h after exposure to PMA (data not shown). Under identical conditions, however, PMA did not induce a significant degree of up-regulation of LFA-1 on BB5 and 82F12. Forty-eight hours after exposure to PMA, the LFA-1 expression on BB5 and 82F12 cells was rather down-regulated. Thus, the inability of 82F12 cells to migrate into the epidermis in vivo was not due to the down-regulation of the LFA-1 upon activation. These results suggest that an increase in motility and adhesiveness of the epidermotropic T cells upon activation does not result simply from the quantitative change in LFA-1.

Effects of LFA-1 Up-Regulation Induced by PMA on Epidermotropic Migration To determine whether the LFA-1 up-regulation after exposure to PMA could render C10 cells capable of migrating into the epidermis in vivo, C10 cells exposed to PMA for 48 h were tested for their ability to migrate into the epidermis upon intradermal inoculation. Because PMA has been shown to activate T cells through direct stimulation of PKC [21], it was possible that after exposure to PMA, C10 cells could be rendered epidermotropic as the result of activation of PKC, independently of their up-regulation of LFA-1. As control experiments, therefore, BB5 cells similarly exposed to PMA were also injected into the footpads of syngeneic and allogeneic mice with or without relevant I-A antigens. The results of the experiments are shown in Table III. Even after exposure to PMA for 48 h, C10 cells remained non-epidermotropic, despite levels of LFA-1 expression comparable to that on J403 cells. The extent of epidermal invasion of PMA-treated BB5 cells was not different from that of untreated BB5 cells. PMA-treated BB5 cells, however, showed epidermotropic migration not only in mice with relevant I-A antigens, but also in those with irrelevant I-A antigens. Similar loss of I-A antigen specificity in the epidermotropic migra-

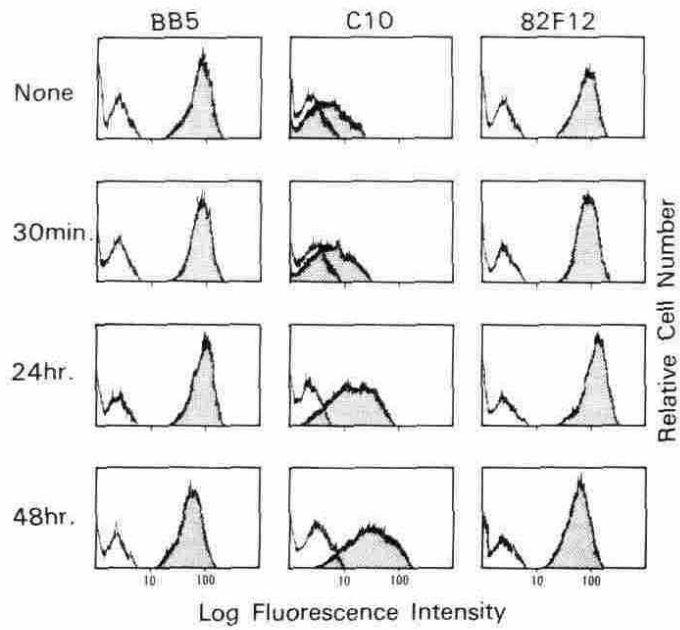

Figure 2. Flow cytometric analysis of modulation of LFA-1 expression by T-cell clones incubated with or without PMA (50 ng/ml) for various time periods. Each histogram shows the analysis of 5,000 cells. *Thin lines* represent control staining with nonrelevant primary MoAb, followed by FITC-conjugated second Ab.

Table III. Effects of PMA Treatment on Epidermotropic Migration

Injected T cells	Treatment before injection*	Recipient (I-A)	No. lymphoid cells invading epidermis†	No. mice with cutaneous GVHD lesions (grade)				
				0	+1	+2	+3	+4
C10	None	B6 (I-A^b)	0	3	0	0	0	0
	PMA	B6 (I-A^b)	0	3	0	0	0	0
	None	Balb/c (I-A^d)	0	3	0	0	0	0
	PMA	Balb/c (I-A^d)	0	3	0	0	0	0
BB5	None	B6 (I-A^b)	119 ± 24	0	0	2	1	0
	PMA	B6 (I-A^b)	100 ± 18	0	1	2	0	0
	None	B10 (I-A^b)	102 ± 33	0	1	1	1	0
	PMA	B10 (I-A^b)	91 ± 25	0	1	2	0	0
	None	Balb/c (I-A^d)	0	3	0	0	0	0
	PMA	Balb/c (I-A^d)	58 ± 21	0	2	1	0	0

* BB5 or C10 cells were cultured for 48 h with or without PMA (50 ng/ml).

† Lymphoid cells within the epidermis were enumerated 96 h after injection of the T cells and are expressed as the mean number per linear millimeter of epidermis. Each group contains three mice.

tion was also observed with BB5 cells exposed to PMA for 1 h (data not shown), and there was no significant difference in the extent of the epidermal invasion between the short-term exposure to PMA and the 48 h exposure. These results indicate that the extent of epidermotropic migration is not related to the magnitude of LFA-1 up-regulation.

DISCUSSION

Epidermotropic migration of T cells resulting in epidermal invasion is a multistep process that is largely dependent on T-cell adhesion to other cells and extracellular matrix proteins. In particular, T-cell adhesion molecules that serve generally to strengthen cell adhesion, such as LFA-1, appear to be primarily involved in such cell-cell and cell-matrix interactions. Several lines of evidence have established that the LFA-1 molecules are required for the adherence of T cells to endothelial cells and epidermal keratinocytes [3–5,24]. Moreover, recent observation that T lymphoblasts adherent to ICAM-1 in artificial membranes were enriched for cells expressing high levels of LFA-1 and CD2 has led to the hypothesis that T cells with higher LFA-1 or CD2 density are more adherent to epidermal keratinocytes expressing ICAM-1 [5]. This hypothesis is supported by our recent observations that epidermal invasion of the cloned T cells with cytolytic activity is blocked by in vivo administration of MoAb to LFA-1 and to CD4 [8]. In addition, treatment of the T cells with anti-LFA-1 MoAb completely abolished their capacity to migrate to the epidermis in vitro [25]. These findings suggest that the ability of the T cells to migrate into the epidermis may depend on their surface expression of LFA-1 and/or other T-cell adhesion molecules. However, there has been no direct evidence that the differences in epidermotropism of T cells reside in the different levels of the T-cell adhesion molecules expressed on their cell surface. The availability of various cloned T cells, with identical antigen specificities and functions but with variable epidermotropic capacities, has provided us with a unique opportunity to assess the role of the T-cell adhesion molecules in epidermotropism of T cells.

In this report, we have shown that the LFA-1 molecule is preferentially expressed on the surface of epidermotropic T cells. The levels of the LFA-1 expressed on the surface of the T cells in the resting state appeared to be related to the ability of the T cells to migrate into the epidermis in vivo, with an exception of clone 82F12. The migratory potential is apparently independent on levels in CD3, CD4, and CD2 expression. These results, together with the documented functional role for LFA-1 in vitro [3–5], suggest that the interaction of the LFA-1 molecule on the T cells with its ligand on other cells or extracellular matrix is involved in epidermotropism of T cells. It should also be noted, however, that the levels of LFA-1 expression of the T-cell surface are not the sole determinant of T-cell epidermotropism, because 82F12 cells, despite intense LFA-1 expression comparable to that of BB5 cells, are incapable of migrating into the epidermis in vivo. Because it has been reported that sialic acid content on lymphocytes is associated with their homing capacity [27], and sialylation heterogeneity of LFA-1 exists among various lymphocyte lines [28], the difference in the ability of T-cell clones with comparable levels of LFA-1 to migrate into the epidermis may reflect differential sialylation of LFA-1 on the T-cell clones. Alternatively, considering the lack of cytotoxic activity in 82F12 cells, it may be that epidermotropism is a sole property of cytotoxic T cells expressing high levels of LFA-1.

It is also possible that other as-yet-unidentified molecules coordinately expressed with LFA-1 may contribute in part to the specific cell-cell or cell-matrix adhesions necessary for the epidermotropic migration. Because keratinocytes have been shown to release various cytokines that can induce a chemotactic response [18,29], differential expression of receptors specific for the keratinocyte-derived cytokines may also play a role in epidermotropism of the T cells. Considering the documented capacity of keratinocyte ICAM-1 to bind T cells expressing LFA-1 [5], it was conceivable that, in addition to their own expression of LFA-1, epidermotropic T cells might be endowed with the capacity to induce keratinocytes to express ICAM-1, thus enabling them to bind the T cells expressing LFA-1. To test this possibility, we attempted to determine whether ICAM-1 could be expressed on epidermal keratinocytes prior to epidermal invasion of the epidermotropic T cells. In the preliminary experiment, however, we were unable to detect any cells in the epidermis that stained with a MoAb against human ICAM-1, RR1/1. Thus, it remains to be elucidated whether epidermotropic T cells can induce the LFA-1 ligand on keratinocytes, until MoAb against a murine analogue of ICAM-1 becomes available.

PMA enhances various types of cell adhesions shown to be LFA-1-dependent [17]. It has not been, however, conclusive whether the increase in cell adhesion induced by PMA or other stimuli is accompanied by the increase in the surface expression of LFA-1 [22,23]. Nickoloff et al showed that treatment of T cells with PMA significantly increased T-cell adhesion to IFN-γ-treated keratinocytes without affecting the quantity of LFA-1 molecules expressed on the T-cell surface, although this adhesion was LFA-1-dependent [26]. Thus, whether the up-regulation of LFA-1 and the increased cell adhesion are causally related is still unknown. Our results demonstrate that after prolonged exposure to PMA C10 cells, despite their up-regulation of LFA-1, remained incapable of migrating into the epidermis, and that BB5 cells failed to up-regulate LFA-1 upon activation with PMA or antigens (data not shown), while they require activation to migrate into the epidermis. Taken together, these results suggest that the presence of high levels of LFA-1 on T cells is absolutely necessary for their epidermotropic migration, but its up-regulation is neither necessary nor sufficient to trigger the epidermotropic migration. It is therefore unlikely that upon stimulation with specific antigens, epidermotropic T cells up-regulate LFA-1 on the cell surface, thereby rendering them more

adherent to other cells. Because BB5, SK1, and J403 cells are stable cell lines with high levels of LFA-1 expression, it is possible that high levels of LFA-1 expression, regardless of cell activation, may be required to mediate stable cell adhesions leading to epidermotropic migration. In other words, high levels of LFA-1 expression may be a constitutive property of epidermotropic T cells that do not require further antigenic stimulation to become adhesive to other cells, while non-epidermotropic T cells only become adhesive after antigenic stimulation, which is yet insufficient to become epidermotropic. Epidermotropic migration may be observed only when a threshold level of LFA-1 expression on the T cells is achieved in a constitutive fashion.

Our previous studies have shown a requirement for activation of the epidermotropic T cells with specific antigens in order to migrate into the epidermis [6–8,18]. The epidermotropic migration is thus likely to be induced by stimulation of TCR/CD3 complex. PMA has been shown to mimic the signals normally delivered by the binding of antigens to the TCR/CD3 complex [21]. Consistent with this view is our present observation that BB5 cells exposed to PMA did not require further antigenic stimulation in situ to migrate into the epidermis: PMA-treated BB5 cells were capable of migrating into the epidermis, even in the recipients, without relevant I-A antigens, while untreated BB5 cells failed to migrate into the epidermis. Recently PMA has been shown to cause an increase in lymphocyte F-actin, which may provide contractile force for functions such as chemotactic movement [30]. This raises the interesting possibility that PMA may induce changes in the conformation or distribution of cytoskeletal proteins in the T cells necessary for the epidermotropic migration, without the intracellular signals generated via TCR/CD3 complex. Thus, studies to clarify the association between cytoskeletal proteins and T-cell adhesion molecules will be an interesting subject for our future work.

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